# 第39章
# ADRENOCORTICOSTEROIDS & ADRENOCORTICAL ANTAGONISTS

## ◆ Adrenocortical Hormones

→屬steroid類結構

→由adrenal cortex生成與分泌

→用來診斷與治療 adrenal function disoders

→secretion control: ACTH

→pharmacologic value: anti-inflammatory agents

# I. ADRENOCORTICOSTEROIDS

**1. Adrenal gland分:**

(1) Adrenal medulla→Epi

(2) Adrenal cortex 分三層 (佔重量的90%)

(a) Zona glomerulosa 球狀層(上層)→Aldosterone

(b) Zona fasciculata 絲狀層(中層)→Cortisol

(佔腎上腺重量的75%)

(c) Zona reticularis 網狀層(下層)→Androgen,Estrogen

**2. Adrenal cortex 可製造cortisol (hydrocortisone, compound F) 它是體內主要endogenous glucocorticoid.**

**3. Cortisol 是維持生命所必須的。**

4. Hypothalamic-pituitary-adrenal axis對於循環中 cortisol 合成 corticosteroid皆有敏感之負性迴饋作用。

(如血中glucocorticoid↑,則可藉著降低正常內生性cortisol 之產生，減低 hypothalamic-pituitary-adrenal axis 之活性。)

**5. Cortisol 由於具有消炎及血糖↑**

∴又叫Glucocorticoids

合成叫做Corticosteroids

·cortisol (hydrocortisone, compound F)

**6.長期服用合成corticosteroid後，突然停藥會造成**

**endogenous及exogenous glucocorticoid 同時缺乏，會嚴重危及生命，造成嚴重病態而死亡。**

**7.外給的corticosteroid必須以極慢的速度減低劑量。**

**8. 醛固酮Aldosterone亦是由腎上腺皮質分泌，主要功能為調節細胞外液的volume及控制鉀離子的代謝。**

∴又叫做 Mineralocorticoids

**9. Glucocorticoids及Mineralcorticoids之主要醫療用途:**

(1) adrenal insufficiency時，可作為 cortisol 之代用品

(2)長或短期抗炎症或免疫抑制作用

(3)治療骨髓增生性疾病 (myeloproliferative disease) ，其他惡性病 (malignancies) 或腦水腫 (brain edema)

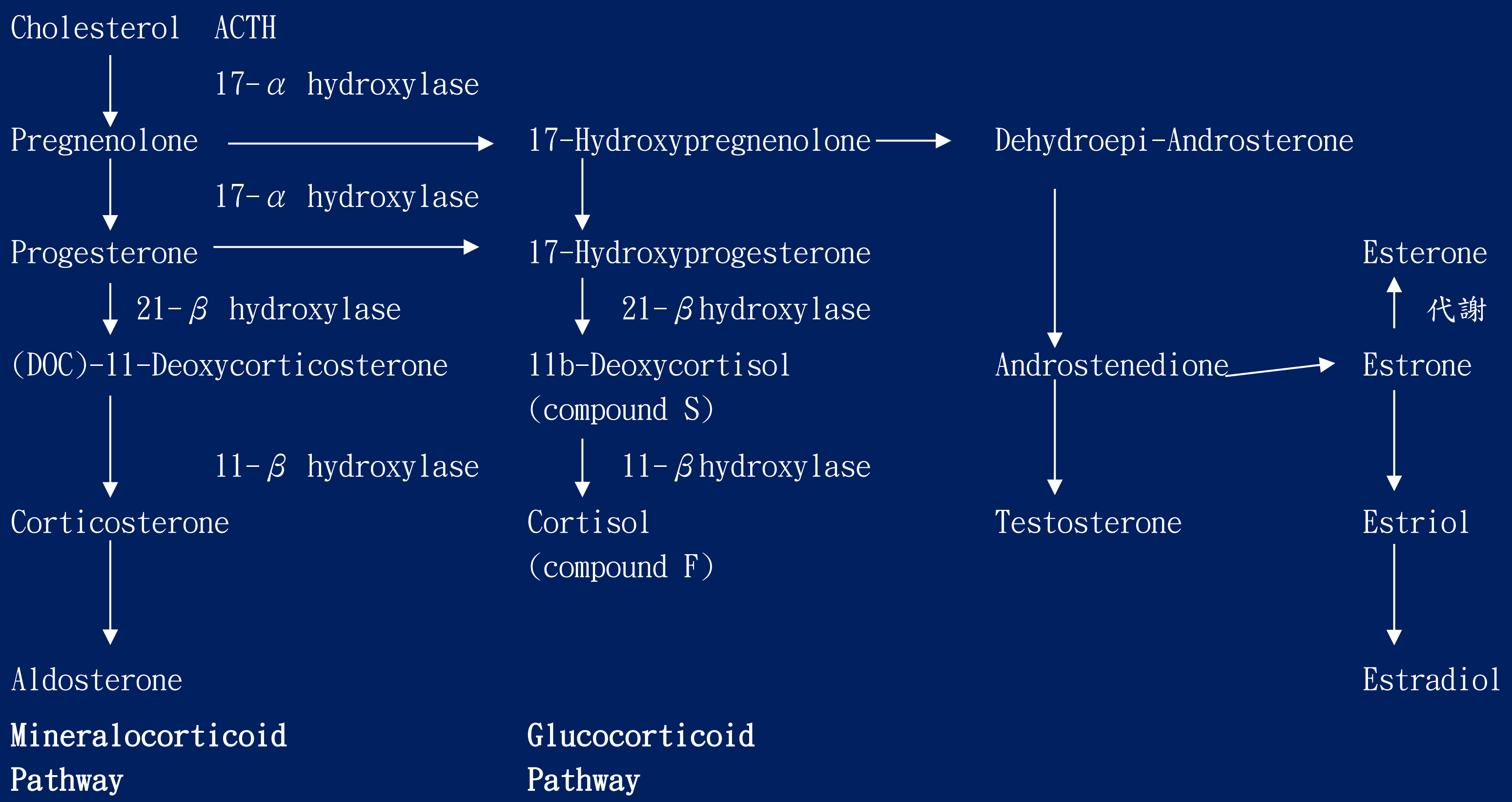
(4)腎上腺功能不足時可作為 aldosterone 的代用品。

## 一、The Naturally Occurring Glucocorticoids; Cortisol (Hydrocortisone)

■ Pharmacokinetics:

1.Adrenocortical hormone biosynthesis

※ Hench,Kendall,Reichstein 氏研究分離及合成，而得到Nobel Prize。




(1) Pregnenolone 是 Corticosterone 及 Aldosterone之Precursor.

(2) 17-hydroxypregnenolone是cortisol 之前驅物。

(3) Metyrapone為11β-hydroxylase inhibitor

∴cortisol及corticosterone合成↓

.

## 一、The Naturally Occurring Glucocorticoids; Cortisol (Hydrocortisone)

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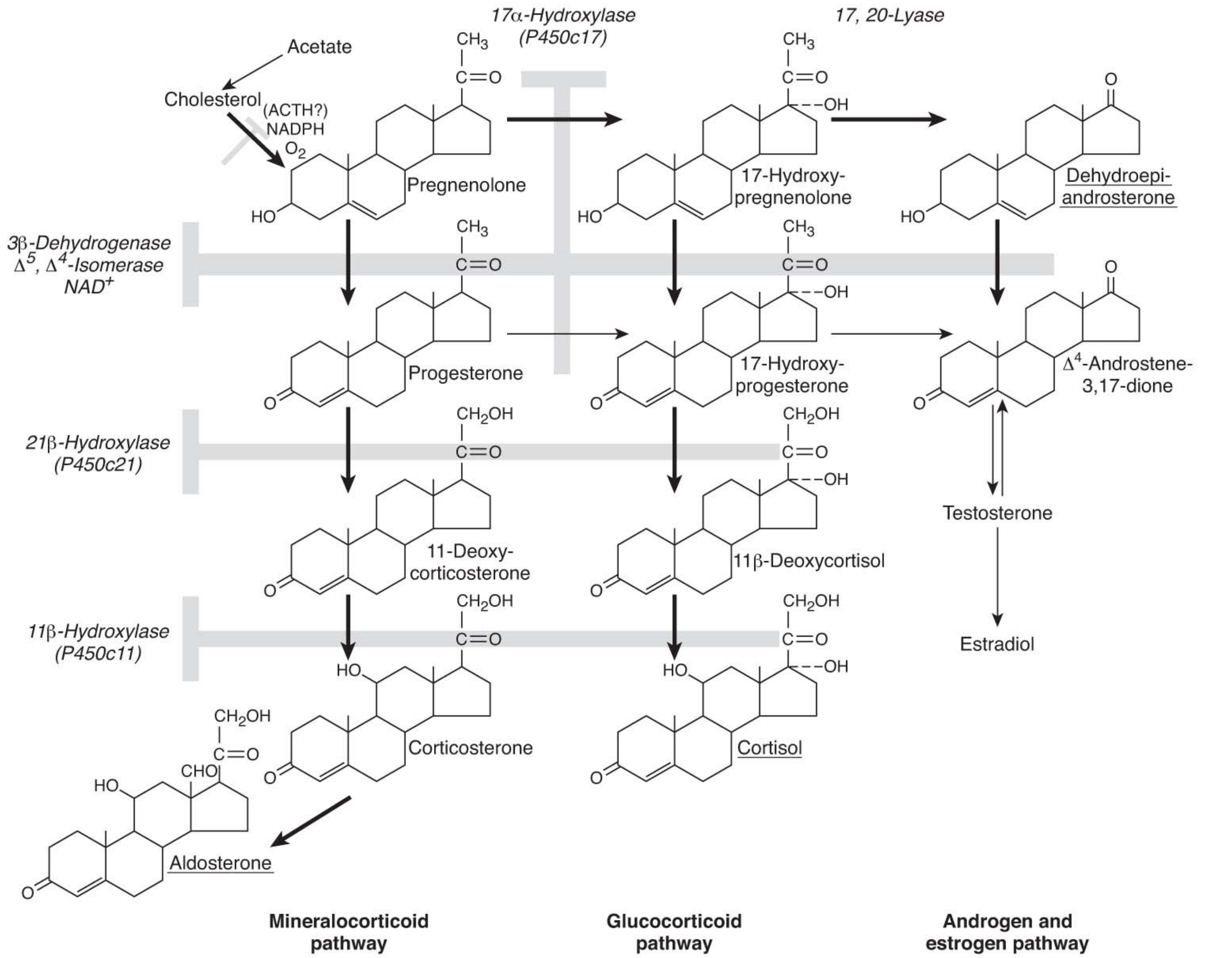


**FIGURE 39–1** Outline of major pathways in adrenocortical hormone biosynthesis. The major secretory products are underlined. Pregnenolone is the major precursor of corticosterone and aldosterone, and 17-hydroxypregnenolone is the major precursor of cortisol. The enzymes and cofactors for the reactions progressing down each column are shown on the left and across columns at the top of the figure. When a particular enzyme is deficient, hormone production is blocked at the points indicated by the shaded bars. (Modified after Welikey et al; reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 17th ed. Originally published by Appleton & Lange. Copyright © 1995 by The McGraw-Hill Companies, Inc.)

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∴ cortisol及corticosterone合成↓

## 2. Transport in Blood (cortisol)

→ cortisol 正常人血漿8 μg/100ml左右，

於清晨未醒之前即開始分泌，然後一直到夜晚，

以增強人體防禦機能及維持生存之功效。

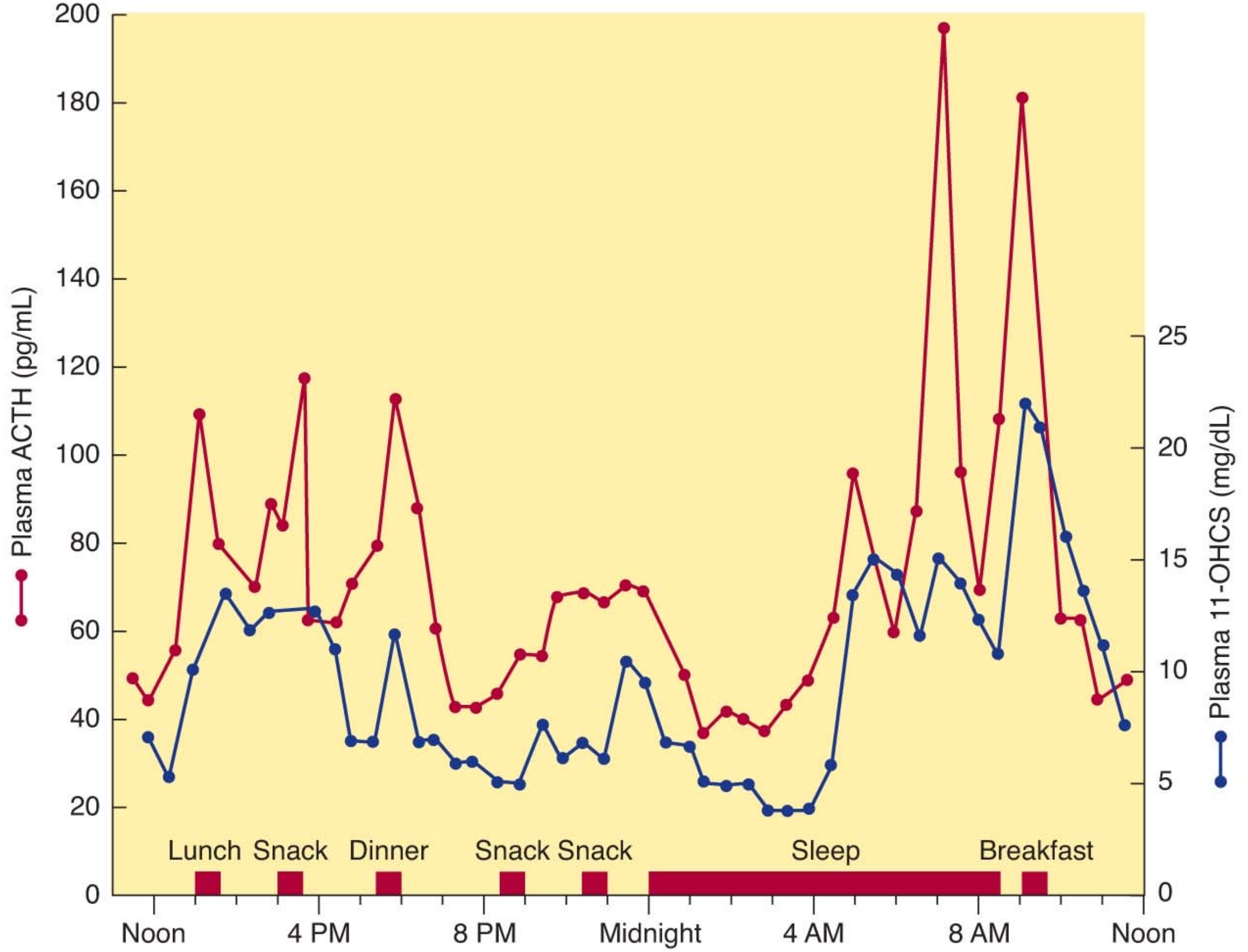



**FIGURE 39–2** Fluctuations in plasma ACTH and glucocorticoids throughout the day in a normal girl (age 16). The ACTH was measured by immunoassay and the glucocorticoids as 11-oxysteroids (11-OHCS). Note the marked ACTH and glucocorticoid rises in the morning, before awakening from sleep. (Reproduced, with permission, from Krieger DT et al: Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrinol Metab 1971;32:266.)

→cortisol 分泌於循環系統內。正常(無壓力)每天分泌10-20ng,

與血漿蛋白結合 (可逆性之結合) corticosteroid-binding globulin (CBG), 又叫transcortin

→cortisol 與globulin之affinity 高，

cortisol 與serum albumin 之 afffinity 很低。

→CBG 為$\alpha_2$-globulin 於肝合成之。

→75% 與CBG結合

15% 與Albumin 結合

10% 為unbound，具有生物活性

→正常16歲女孩血中ACTH變化

**3. Cortisol 於循環中之 $t_{1/2}$ = 60-90 min**

其$t_{1/2}$之增長是由於:

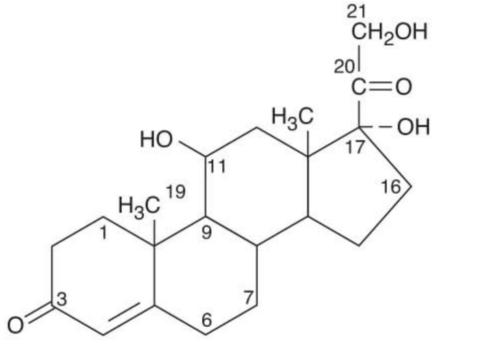
(1) 服用大量cortisol

(2) stress

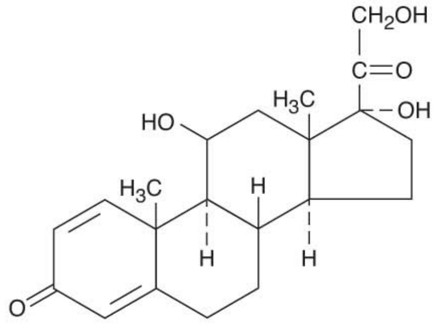
(3) hypothyroidism

(4) 肝病

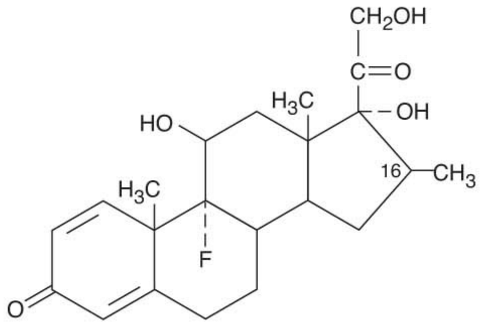
**4. Glucocorticoids之化學構造式**



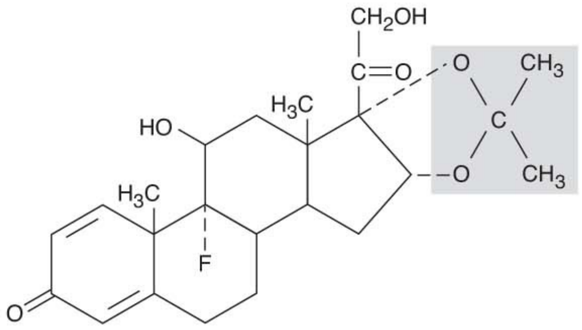

**Cortisol** (hydrocortisone)




**Prednisolone**




**Betamethasone**




**Triamcinolone** (acetonide moiety shaded)

**FIGURE 39–3** Chemical structures of several glucocorticoids. The acetonide-substituted derivatives (eg, triamcinolone acetonide) have increased surface activity and are useful in dermatology. Dexamethasone is identical to betamethasone except for the configuration of the methyl group at $C_{16}$: in betamethasone it is beta (projecting *up* from the plane of the rings); in dexamethasone it is alpha.

## ■ Pharmacodynamics (cortisol):

### A. Mechanism of Action

glucocorticoids

→diffuse or 與細胞膜上之cytoplasmic glucocorticoid receptor-heat- shock protein complex bind

→此大分子 complex 形成之後→進入nucleus

→glucocorticoid response elements (GREs)

再與chromosomal 成分相互作用→改變基因gene，包括:

∴改變 enzyme之合成及活性

改變 membrane permeability

改變 transport processes 及構造

→產生引起最後hormone 反應之蛋白質

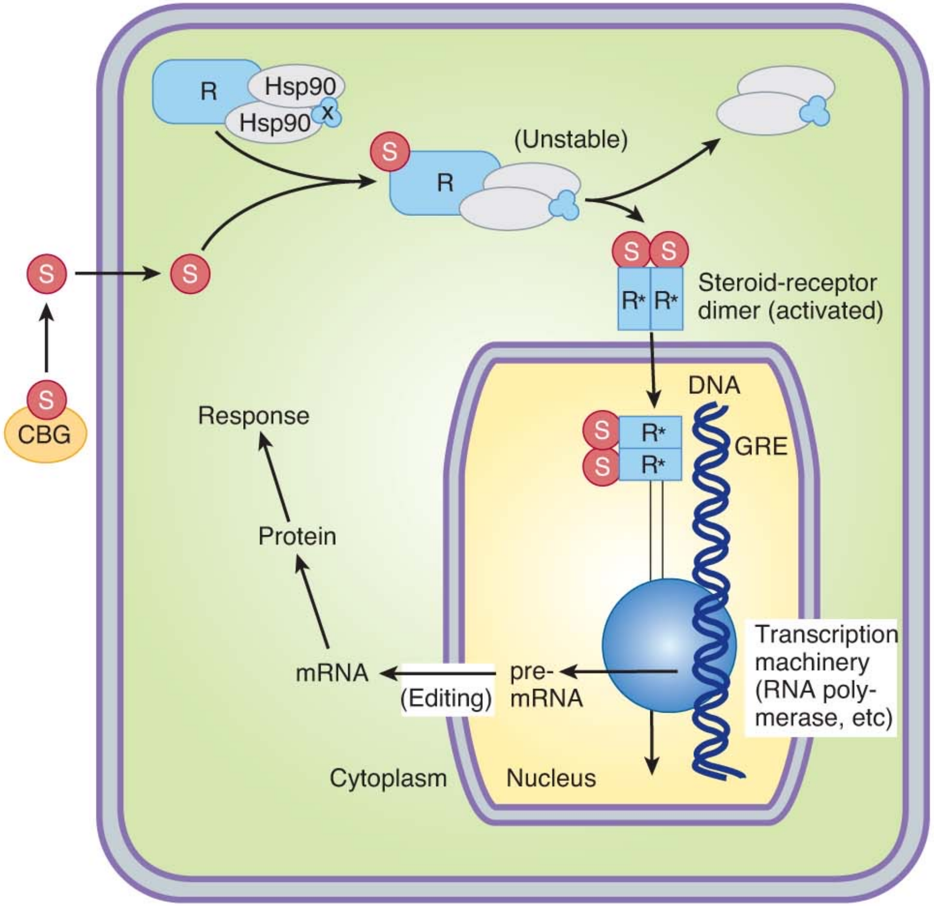



**FIGURE 39–4** A model of the interaction of a steroid, S (eg, cortisol), and its receptor, R, and the subsequent events in a target cell. The steroid is present in the blood in bound form on the corticosteroid-binding globulin (CBG) but enters the cell as the free molecule. The intracellular receptor is bound to stabilizing proteins, including two molecules of heat shock protein 90 (Hsp90) and several others, denoted as "X" in the figure. This receptor complex is incapable of activating transcription. When the complex binds a molecule of cortisol, an unstable complex is created and the Hsp90 and associated molecules are released. The steroid-receptor complex is now able to dimerize, enter the nucleus, bind to a glucocorticoid response element (GRE) on the regulatory region of the gene, and regulate transcription by RNA polymerase II and associated transcription factors. A variety of regulatory factors (not shown) may participate in facilitating (coactivators) or inhibiting (corepressors) the steroid response. The resulting mRNA is edited and exported to the cytoplasm for the production of protein that brings about the final hormone response. An alternative to the steroid-receptor complex interaction with a GRE is an interaction with and altering the function of other transcription factors, such as NF-κB in the nucleus of cells.

# ■ Pharmacodynamics (cortisol):

## B. Physiologic effects (cortisol):

→*血管及氣管平滑肌如無 cortisol 存在
對catecholamine 之反應即減低;

→*fat cell對catecholamines, ACTH; GH 之 lipolytic response;
如無 cortisol 存在，反應即減弱。

→*如: cortisol 存在即回復 (治療休克)

## C. Metabolic effects:新陳代謝

**1. 增加Gluconeogenesis↑(葡萄糖新生)**

→∴造成肝醣堆積於肝臟，

→血糖↑，另刺激insulin釋放

此血糖↑，會使糖尿病惡化或誘發D.M.

叫做Adrenal diabetes

**2.增加 lipolysis**

(因cortisol 抑制葡萄糖經由fat cell 之再吸取 uptake)

但因如上會造成insulin↑

* insulin為antilipolytic agent

∴會造成淨值即增加 fat deposition (堆積)

→fatty acid 及glycerol進入循環中

此現象尤其發生於禁食狀況。

## D. Catabolic and Antianabolic effects (異化及抗同化作用)

·Catabolic effect 異化作用即表示分解作用 (蛋白質分解→胺基酸)

·Anabolic effect 同化作用即表示合成作用 (蛋白質合成)

·雖然 glucocorticoids 在肝臟能刺激 RNA及protein合成。

但因在淋巴樣 (lymphoid) 及結締組織、肌肉、末梢脂肪及皮膚有異化及抗同化作用。

∴如服用超過生理量之 glucocorticoids

→肌肉量減少↓及虛弱。

→皮膚變薄。

·對bone之異化及抗同化作用是 Cushing syndrome ，發生骨鬆症

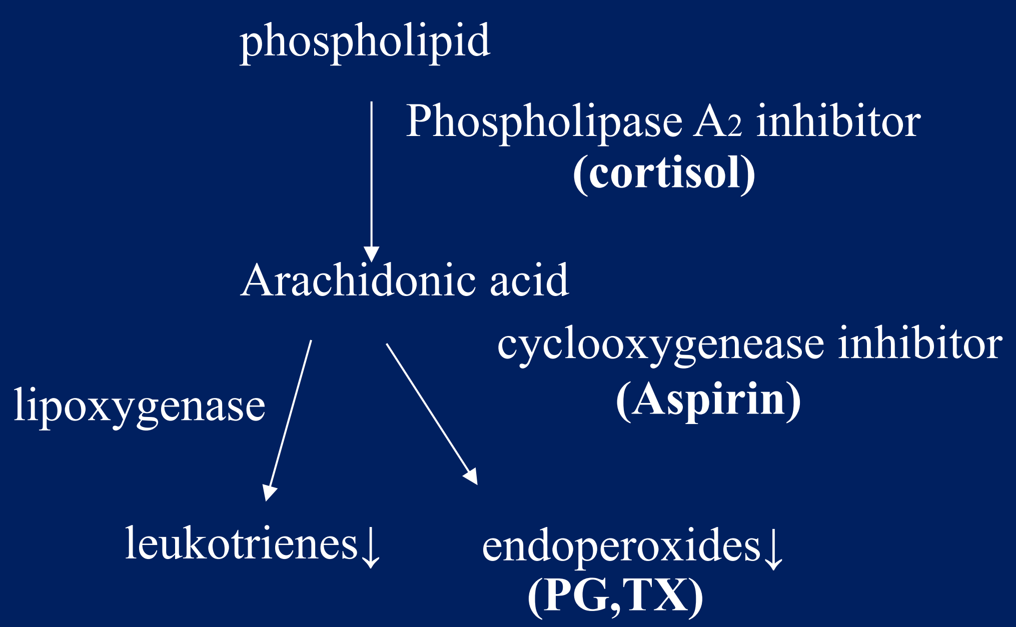
(osteoporosis) 之原因。

·因此限制 glucocorticoids 長期服用 。

·影響小孩生長 (給高劑量GH可部份防止)

# E. Anti-Inflammatory & Immunosuppressive Effects

## 1. Cortisol 抑制 phospholipase A2 之活性



## E. Anti-Inflammatory & Immunosuppressive Effects

**2. 服用corticosteroid會抑制白血球聚集在發炎地區**

∴造成淋巴組織之衰退及萎縮，

減少monocytes，eosinophils，及basophils↓

宿主之defense mechanism降低↓

## F. 治療劑量下:

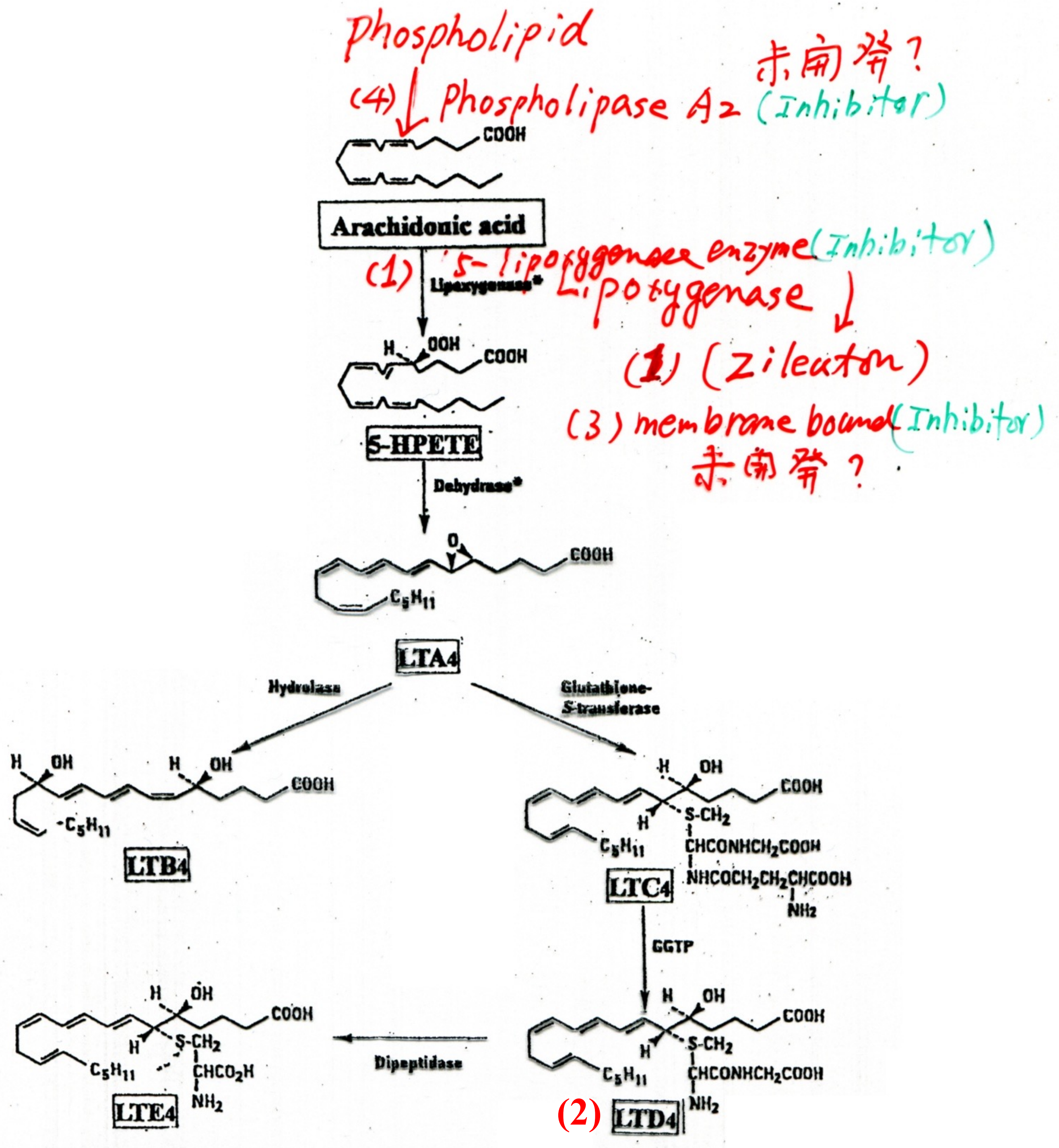
glucocorticoids會降低腦下腺前葉生長激素的分泌

*長期接受glucocorticoid治療兒童，生長受阻，可是血中生長激素及somatomedin C 均正常。

## G.目前認定 glucocorticoid 對生長抑制作用可能是

(1)直接抑制somatomedin C之作用或，

(2)促進肝臟中Somatomedin C inhibitor 之release



Phospholipid
(4) Phospholipase A2 (Inhibitor)
COOH
Arachidonic acid
(1) 5-lipoxygenase enzyme (Inhibitor)
Lipoxygenase
(1) (Zileuton)
(3) membrane bound (Inhibitor)
H
OOH
COOH
5-HPETE
Dehydrase*
O
COOH
C5H11
LTA4
Hydrolase
Glutathione-S-transferase
H
OH
COOH
-C5H11
LTB4
S-CH2
CHCONHCH2COOH
NHCOCH2CH2CHCOOH
NH2
LTC4
GGTP
LTD4
(2)
Dipeptidase
CHCO2H
LTE4

**$LTC_4$&$LTD_4$:**

為強力支氣管收縮劑，過敏緩慢作用物質之一

作用藥物類型:

(1) 5-lipoxygenase enzyme inhibitor: Zileuton

(2) Leukotriene receptor antagonist:

Zafirlukast, montelukast

(3) Inhibitors of an importan membrane-bound 5-lipoxygenase activating protein (未開發)

(4)Phospholipase $A_2$ inhibitors (未開發)

## COX-1 & COX-2 inhibitors

| COX-1 inhibitors | COX-2 inhibitors |
|---|---|
| Indomethacin<br>Sulindac | Celecoxib<br>Rofecoxib |

## Nonselective COX inhibitors

| |
|---|
| Meclofenamate<br>Ibuprofen |

- COX-2 inhibitors 較不影響胃液分泌，適用於慢性發炎

# COX-1 & COX-2

| COX-1 | COX-2 |
| --- | --- |
| 存在、廣泛分布<br>Housekeeping function<br>胃壁細胞保護功能 | 誘發產生<br>於發炎及免疫細胞刺激下<br>產生 |

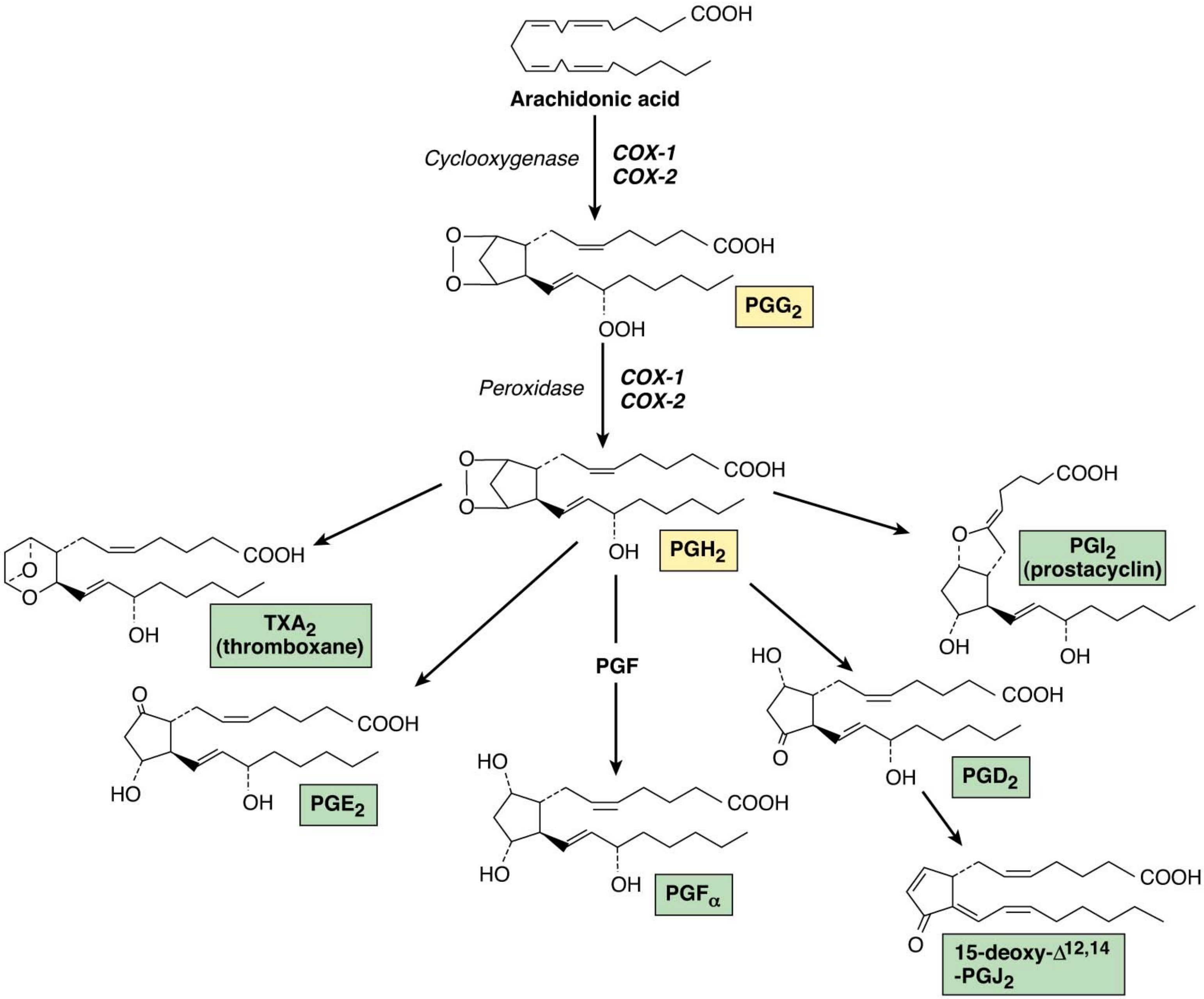



**FIGURE 18–2** Prostanoid biosynthesis. Compound names are enclosed in boxes.

# $TXA_2$ 生理功能

促進血小板凝集及血管收縮，
主要藥物用於心血管系統。

(1) Synthesis inhibitor: Aspirin 長效性抑制血小板
cyclooxygenase 活性

(2) $TXA_2$ antagonist: Sulotroban

**H. Glucocorticoid 會影響腎上線髓質 (adrenal medulla)**

使norepinephrine 轉變成 epinephrine

(即靜脈中cortisol可調節 phenylethanolamine N-methyltransferase)

**I. Other Effects**

(a) 胃酸↑(酸性↑，pepsin↑)→使黏膜變薄 $\xrightarrow{\text{長期}}$ 潰瘍

(b) Euphoria

(c) convulsion 之 threshold ↓

(d) 肌肉無力萎縮(steroid myopathy)

# 二、Synthetic Adrenocorticosteroids

## ■ Pharacokinetics

**A. Source:**

1. 現在都用合成，希望消炎↑，鈉滯留↓，水腫↓，
合成者叫Corticosteroid。

2. 可從動物牛之 cholic acid，或植物之 steroid sapogenins，
diosgenin (Liliaceae, Dioscoreaceae)

3. (1) 短效 Hydrocortisone, Prednisolone.
(2) 中效 Paramethasone.
(3) 長效 Betamethasone, Dexamethasone.

# 山 藥(本經)

一. 功效：補脾胃、益肺腎

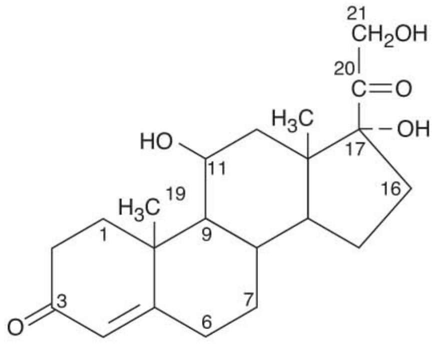
二. 1937年Reichstein 和Von Euw兩人從薯蕷皂苷元(diosgenin)合成 desoxycorticosterone，並證實它存在於腎上腺。從此很多研究開始探討腎上腺素維持生命扮演的角色。

三. 1949年 Hench用可體松治療風濕性關節炎獲得驚人的效果，為皮質類固醇的研發立下新的里程碑。

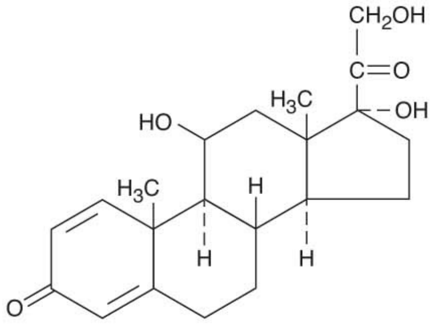
四. 2009年邱傳淞等研究發現基隆山藥及diosgenin具有抗衰老作用。

薯蕷 *Dioscorea opposita* Thunb.

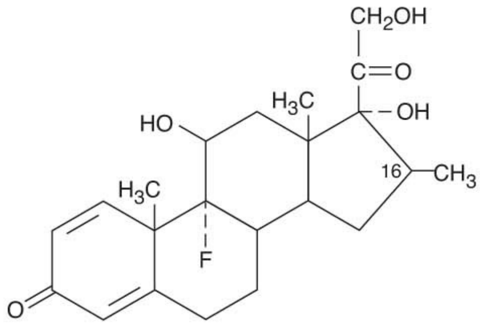
藥材山藥 Rhizoma Dioscoreae



**Cortisol** (hydrocortisone)



**Prednisolone**



**Betamethasone**

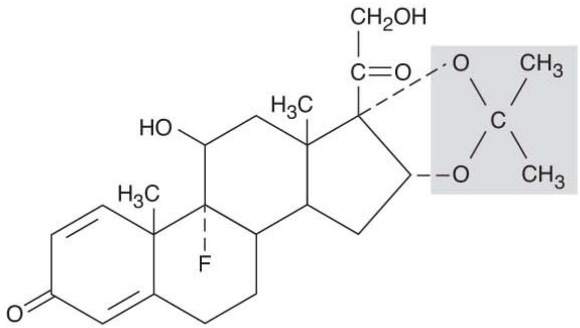


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**TABLE 39–1** **Some commonly used natural and synthetic corticosteroids for general use.**

| | Activity[1] | | | | |
|---|---|---|---|---|---|
| **Agent** | *Anti-Inflammatory* | *Topical* | *Salt-Retaining* | **Equivalent Oral Dose (mg)** | **Forms Available** |
| **Short- to medium-acting glucocorticoids** | | | | | |
| Hydrocortisone (cortisol) | 1 | 1 | 1 | 20 | Oral, injectable, topical |
| Cortisone | 0.8 | 0 | 0.8 | 25 | Oral |
| Prednisone | 4 | 0 | 0.3 | 5 | Oral |
| Prednisolone | 5 | 4 | 0.3 | 5 | Oral, injectable |
| Methylprednisolone | 5 | 5 | 0.25 | 4 | Oral, injectable |
| Meprednisone[2] | 5 | | 0 | 4 | Oral, injectable |
| **Intermediate-acting glucocorticoids** | | | | | |
| Triamcinolone | 5 | 5[3] | 0 | 4 | Oral, injectable, topical |
| Paramethasone[2] | 10 | | 0 | 2 | Oral, injectable |
| Fluprednisolone[2] | 15 | 7 | 0 | 1.5 | Oral |
| **Long-acting glucocorticoids** | | | | | |
| Betamethasone | 25–40 | 10 | 0 | 0.6 | Oral, injectable, topical |
| Dexamethasone | 30 | 10 | 0 | 0.75 | Oral, injectable, topical |
| **Mineralocorticoids** | | | | | |
| Fludrocortisone | 10 | 0 | 250 | 2 | Oral |
| Desoxycorticosterone acetate[2] | 0 | 0 | 20 | | Injectable, pellets |

【NOTE】:

- **影響 Glucocorticoids 治療活性最重要之藥物動力學因素:**

  1.從給藥部位 (消化道、皮膚、吸入) 之吸收速率

  2.血漿中半衰期 (受到血漿中cortisol-binding globulin 的影響或其代謝速率受到肝臟酵素的影響)

  3.藥物之生物可用率 (bioavailability)

- **Glucocorticorids 只有在第11個碳上有hydroxy group時才有活性，**

  因此cortisone在活體內hydroxylation→cortisol

  prednisone→prednisolone 才有活性

- 大部份glucocorticoids在G-I tract 很快被吸收，但由皮膚吸收則依不同製劑而有差異。通常皮膚吸收很慢，不會有藥物蓄積情形。

## ■ Clinical Pharmacology (cortisol)

### A. Diagnosis and Treatment of Disturbed Adrenal Function:

#### 1. Adrenocortical Insufficiency

(1) Chronic (Addison’s disease)

→特性: 有hyperpigmentation, weakness, fatigue, weight loss, B.P.↓,

當飢餓時不能維持血糖之濃度。

→·由Adrenal 不足者叫做Primary (Addison’s disease).

·由hypothalamic-pituitary不足者叫做Secondary.

→·診斷: 給予ACTH

⇒Primary: cortisol,corticosteroids 分泌不增

Secondary: cortisol,corticosteroids↑↑

→Primary 或腎上腺切除者

每天給30mg cortisol 可以改善

(2)Acute: Cortisol phosphate100 mg I.V. q6h

直至病人安定 stable

## 2. Adrenocortical hyperfunction

a. congenital adrenal hyperplasia(先天性增生)

如: 21-hydroxylase 減少或缺少

**17-hydroxyprogesterone** $\xrightarrow{\textbf{21-hydroxylase}}$ **11β-Deoxycortisol→cortisol**

→減少或缺少 21-hydroxylase 時cortisol即↓

∴ACTH release ↑

造成腎上腺增生 adrenal hyperplasia

另亦會造成 17-hydroxyprogesterone↑

則Androgen↑發生男性化

→治療腎上腺先天性增生，

可給予Cortisone 25~100 mg/天 I.M.

for 5~10 天，然後4-6 mg/天。

# b. Cushing Syndrome:

* 由於二側腎上腺增生，造成Pituitary adenoma (腺瘤)，

 又叫Cushing Disease。

* 特徵: 大圓臉及肥胖體形。

* 治療: 以外科切除 tumor，然後再給予大量 300 mg

 hydrocortisone I.V. 點滴。

**c. 治療 Shock:**

cortisol 能恢復 C.O.，而reverse hypotension.

(因能使存在於心、血管之Adrenergic receptor

對CA 之 Sti.敏感度↑)

**d. Aldosteronism:**

* 原因:

1. adrenal adenoma→aldosterone↑
2. hyperplastic glands (malignant tumor) →不正常分泌

* 臨床症狀:

hypertension, polyuria, polydipsia, weakness

renal potassium loss導致hypokalemia, alkalosis, hypernatremia

# d. Aldosteronism:

* 這些Syndrome 是由於

  adrenal steroid不正常合成，而過度分泌如下物質:

  ↑↑desoxycorticosterone, ↑corticosterone,

  18-hydroxycorticosterone↑

* **Secondary aldosteronism:**

  low level of plasma renin activity & angiotensinII

* **Treatment:**

  desoxycorticosterone acetate (20 mg/kg i.m. For 3 days)

  fludrocortisone (0.2 mg/twice daily p.o.. for 3 days)

  spironolactone

## 3. Use of glucocorticoids for diagnostic purposes:

*** dexamethasone suppression test**

**→Cushing's syndrome**

(1) dexamethasone 1 mg p.o. At 11 PM

→plasma sample in morning

⇒normal: cortisol < 5 μg/dL

Cushing's syndrome:> 10 μg/dL

(2) dexamethasone 0.5 mg/6hrs p.o. For 2 days,

2 mg/6hrs p.o. For 2 days

→urine assayed cortisol or its metabolites (Liddle's test)

or dexamethasone 8 mg at 11 PM

→plasma sample in 8 AM following day

⇒Cushing's syndrome:↓ 50% hormone levels

## B. Corticosteroids and Stimulation of Lung Maturation in the Fetus. (胎兒肺臟成熟之刺激)

- 胎兒的肺臟成熟受胎兒分泌的cortisol 所調節。
- 如母親接受大劑量glucocorticoid治療

  →會減少早產嬰兒呼吸困難徵候群之發病率。

## C. Corticosteroids and Nonadrenal Disorders.

- 合成的cortisol 可用來治療與adrenal function 無關之疾病。如 asthma, allergic reaction, eye disease, edema, skin disease

## TABLE 39–2 Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders.

| Disorder | Examples |
| --- | --- |
| Allergic reactions | Angioneurotic edema, asthma, bee stings, contact dermatitis, drug reactions, allergic rhinitis, serum sickness, urticaria |
| Collagen-vascular disorders | Giant cell arteritis, lupus erythematosus, mixed connective tissue syndromes, polymyositis, polymyalgia rheumatica, rheumatoid arthritis, temporal arteritis |
| Eye diseases | Acute uveitis, allergic conjunctivitis, choroiditis, optic neuritis |
| Gastrointestinal diseases | Inflammatory bowel disease, nontropical sprue, subacute hepatic necrosis |

**TABLE 39–2 Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders.**

| Disorder | Examples |
|---|---|
| Hematologic disorders | Acquired hemolytic anemia, acute allergic purpura, leukemia, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, multiple myeloma |
| Systemic inflammation | Acute respiratory distress syndrome (sustained therapy with moderate dosage accelerates recovery and decreases mortality) |
| Infections | Acute respiratory distress syndrome, sepsis |
| Inflammatory conditions of bones and joints | Arthritis, bursitis, tenosynovitis |
| Neurologic disorders | Cerebral edema (large doses of dexamethasone are given to patients following brain surgery to minimize cerebral edema in the postoperative period), multiple sclerosis |

## TABLE 39–2 Some therapeutic indications for the use of glucocorticoids in nonadrenal disorders.

| Disorder | Examples |
|---|---|
| Organ transplants | Prevention and treatment of rejection (immunosuppression) |
| Pulmonary diseases | Aspiration pneumonia, bronchial asthma, prevention of infant respiratory distress syndrome, sarcoidosis |
| Renal disorders | Nephrotic syndrome |
| Skin diseases | Atopic dermatitis, dermatoses, lichen simplex chronicus (localized neurodermatitis), mycosis fungoides, pemphigus, seborrheic dermatitis, xerosis |
| Thyroid diseases | Malignant exophthalmos, subacute thyroiditis |
| Miscellaneous | Hypercalcemia, mountain sickness |

## ■ 副作用

(1) 胃出血:

∵cortisol 抑制白血球聚集在發炎地區，造成淋巴組織之衰退，

∴降低宿主之 defense mechanism, 即干擾粘膜對酸、Pepsin 消化之protect。

(2) 血糖↑

(3) Osteoporosis 骨鬆症(非可逆性) 能分解骨之母体組織 Collagenous protein matrix: 拮抗Vit D 作用

(4) 拮抗 GH 之分泌，影響小孩生長。

(5) 產生 Cushing syndrome:

體重↑，moon face，血鈉↑，血鉀↓，肌肉無力。

(6) salt retention，psychosis

## ■ 副作用

【NOTE】：

1. 需長期使用GLUCOCORTICOIDS，可選擇intermediate-acting steroids: prednisone，prednisolone，在8:00 AM 給藥，可維持48小時再給藥。
2. long-acting steroids 不可用於alternate day therapy (隔日治療)，會造成藥物蓄積，易生toxicity。

【NOTE】:

## A. Selection of Drugs

1. cortisol 僅用於 endogenous glucocorticosd 製造不足之 adrenal insufficiency (腎上腺功能不足) 的替代治療，不能用於抗發炎治療 (抗發炎效果差)

**2. prednisolone為抗發炎及免疫抑制之第一選擇用藥，可使用於autoimmune disease 如:**

(1) collagen disease (系統性紅斑狼瘡systemic lupus erythematous，多肌炎-皮肌炎polymyositis-dermatomyositis及rheumatoid arthritis)

(2) 脈管炎症候(vasculitos syndromes)如多動脈炎結節polyarteritis nodosa、巨細胞動脈炎giant cell arteritis、韋格納氏肉芽腫Wegener’s granulomatosis。

(3) 消化道發炎

(4) 腎臟自體免疫疾病(如腎絲球腎炎)

※與antiemetics 配合,用於anticancer drugs引起之nause及vomiting

**3. Dexamethasone 及Betamethasone 抗發炎作用最強，血漿中時間亦長，但有明顯的生長抑制作用。**

∴可用於急性給藥，以最大劑量產生抗發炎時使用之，

如敗血性休克 (septic shock)，

或腦水腫 (brain edema)；

但不是長期抗發炎治療之最佳選擇。

4. **Prednisolone 隔日給藥治療 (alternate-day therapy)，**

- **對hypothalamic-pituitary axis 及生長之抑制較小，**

  **其抗發炎之目的仍可達成。**

- **但每日給藥，改為隔日給藥，在不服用prednisolone 那天**

  **會產生 clinical hypocortisolism症狀: 有疲勞、噁心、嘔吐**

  **或hypotension。**

  註：long-action steroids 不可用於 alternate day therapy，

  會造成藥物蓄積，易生toxicity。

## B. Side Effect:

### 1. Glucocorticoid side effect on Calcium metabolism

**在治療量下長期使用糖皮質激素會造成骨質疏鬆症**

**(osteoporosis)**

(1) 降低鈣的吸收及腎對鈣之再吸收

(2)對bone直接作用

(3)阻止calcitonin effect

## 2. Glucocorticoid Side Effect on Calcium Metabolism

(1) 急性對CNS有興奮作用，雖然血中高濃度之glucocorticoid 有euphoria，但慢性hypercortisolism會有depression, 睡眠失調及精神症狀

(2) 增加消化性潰瘍

(3) Glucocorticoid因對於glucose metabolism扮演重要角色而得名，其增加血中glucose方式如下:

(a) 增如肝臟的gluconeogenesis及glucose secretion

(b) 增加肝臟因升糖激素glucagon及catecholamine所引起糖質新生作用之敏感性

(c) 降低週邊組織對glucose之uptake及利用

(d) 增加糖質新生作用原料 (gluconeogenesis substrate)

--如增加肌肉中蛋白質分解及抑制蛋白質合成。

(e) 治療 Shock:

cortisol 能恢復 C.O.，而reverse hypotension.

(因能使存在於心血管之 Adrenergic receptor 對CA之Sti.敏感度↑)

(4) 每日服用5mg，超過2週便會產生抑制 hypothalamic-pituitary adrenal axis 使corticotropin-release hormone分泌不足

(5) 長期服用者

男人: testosterone↓

女人: 干擾排卵，功能失調性子宮出血及月經過少。

# II.Mineralocorticoids (Aldosterone, Deoxycorticosterone,Fludrocortisone)

- **Aldosterone會使mineralocorticoid receptor活化**

  →B.P↑，鈉滯留，使鉀及氫離子由腎排除。

  (高血壓、低鉀性鹼中毒)

- **Aldosterone:**

  1. 係腎上腺Cortex之球狀層(上層)合成。
  2. 對$Na^+$ retention影響最強。
  3. 合成需要 ACTH，

     但調節需要，如循環血量↓，血鈉↓，血鉀↑。
  4. 促進 aldosterone分泌

# II.Mineralocorticoids (Aldosterone, Deoxycorticosterone,Fludrocortisone)

- **Aldosterone:**

  5. 使遠端腎小管$Na^+$ - $K^+$ exchange↑

     ∴使$Na^+$ 再吸收，$K^+$ 排泄

  6. 另angiotensin 係強力刺激 aldosterone 之 production.

  7. aldosterone↑會產生血鈉↑，血鉀↓

     metabolic alkalosis，血量↑，B.P.↑

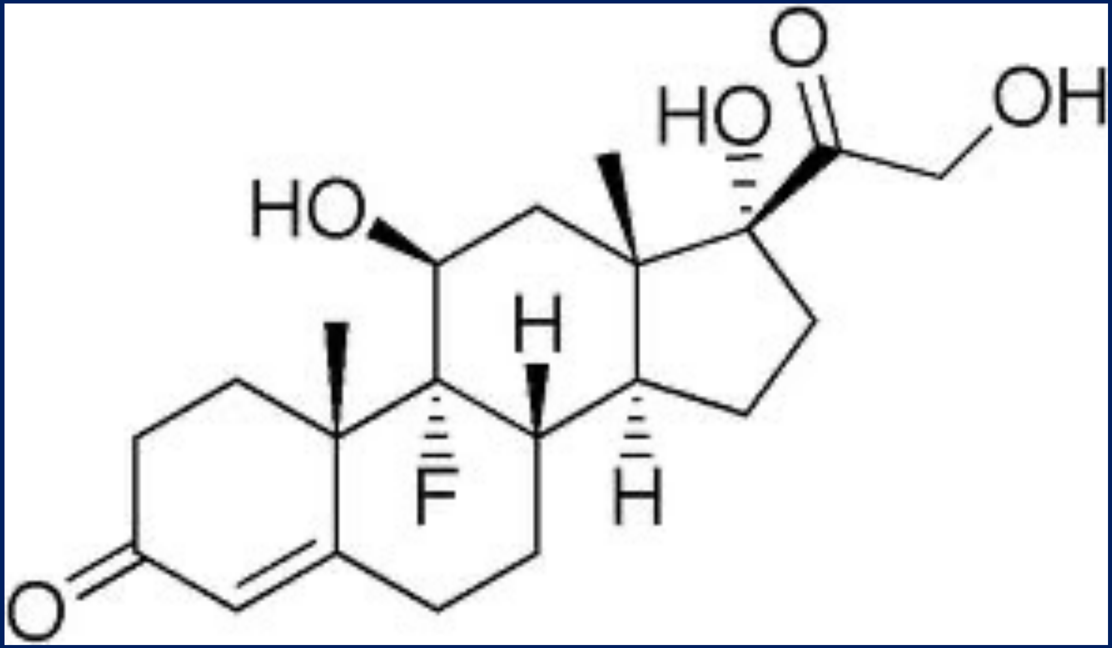
- **DOC: Deoxycorticosterone**

  是aldosterone之前驅物，每天分泌200 μg/天，

  在循環中$t_{1/2}$為70 分。

## ■ Fludrocortisone:

·可同時增強 glucocorticoid，及mineralocorticoid，但對於鹽類皮質固醇作用較顯著，每週 2-7 次，每次 0.1 mg，可強力鈉保留作用，使用於腎上腺機能不足。



# Aldosterone

↙ ↘

腎對鈉之再吸收　增加腎對鉀之排出

↓　↓　↓

血鈉↑　$H^+$ 排出　低血鉀症

↓　↓　↓

Polydipsia　鹼中毒　肌肉無力

↓ 口渴

Hypervolemia

血溶積↑

↓

心輸出↑

↓

B.P.↑

**Triamcinolone: mineralocorticoid activity 較低，且鉀保留作用甚強**

# III. Adrenal Androgens

→ 由adrenal cortex 分泌:

大量: dehydroepiandrosterone (DHEA)

少量: androstenedion, testosterone

→DHEA & DHEAS (DHEA sulfate)

藉由liver enzymes 具重要之代謝作用

抑制體重增加、atherosclerosis (粥狀動脈硬化)、prolong life (animal & humen)

# § ANTAGONISTS OF ADRENOCORTICAL AGENTS

## 一、Synthesis Inhibitors & Glucocorticoid Antagonists

### 1. Mitotane

可減少 corticosteroids↓

∴治療 adrenal tumor 10 g/天，

但毒性大，tremor，(實驗中)。

### 2. Amphenone B

比 mitotane 強，

∴造成ACTH↑，腎上腺增殖，毒性大，影響肝、

甲狀腺功能。

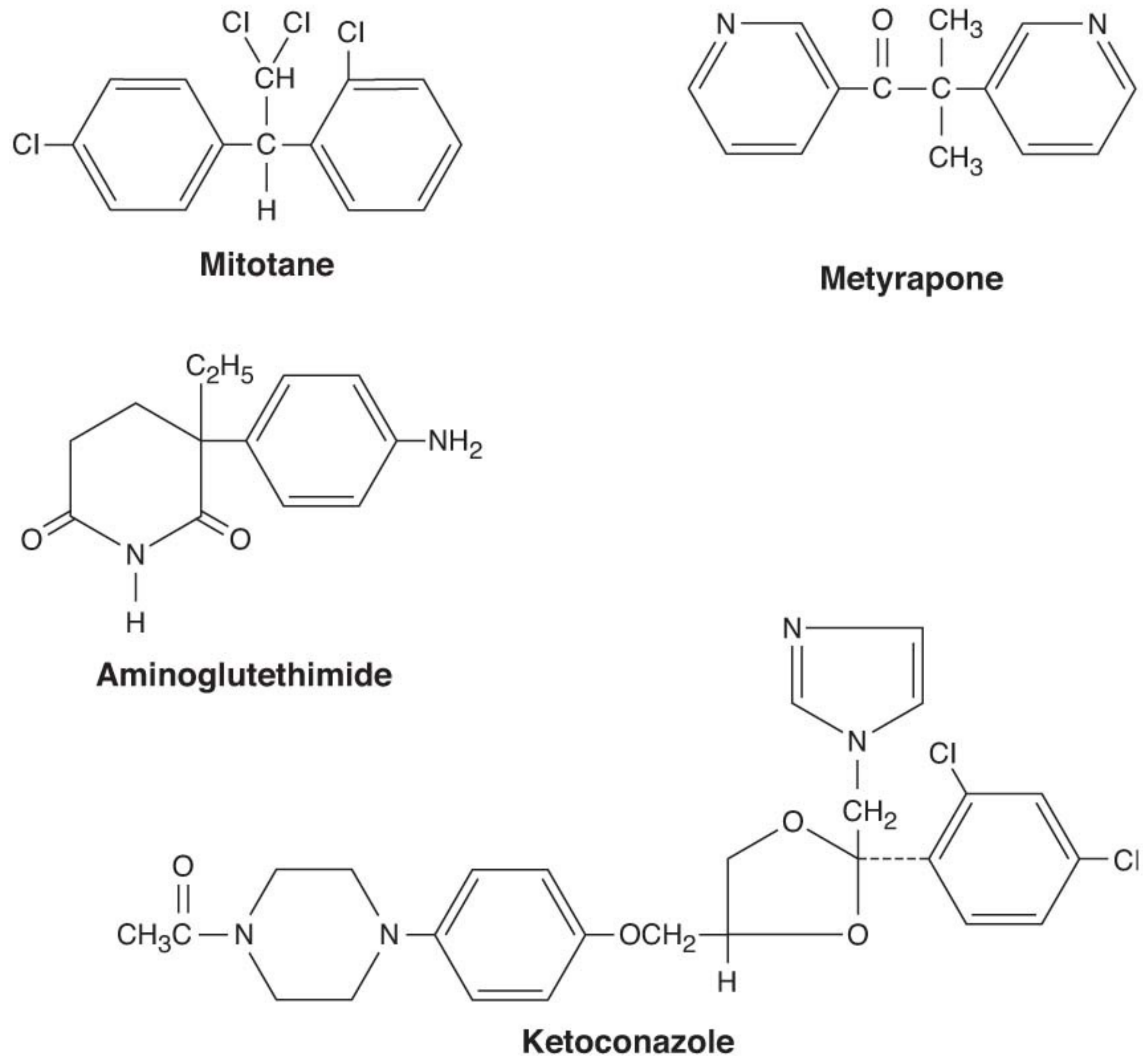



**FIGURE 39–5** Some adrenocortical antagonists. Because of their toxicity, some of these compounds are no longer available in the USA.

## 3. Metyrapone:

具有選擇性抑制 11-hydroxylase，

∴ cortisol 及corticosterone合成↓

11-Deoxycorticorticosterone → corticosterone → Aldosterone

11-Deoxycortisol → cortisol

← 11β-hydroxylase →

(-) Metyrapone

(-) Metyrapone

* 服用 Metyrapone 後，測11-deoxycortisol 或 ACTH量，用來測 Adrenal function

# 4. Aminoglutethimide

係抑制 cholesterol 轉換成 pregnenolone

∴所有激素合成皆被減低，因此與dexamethasone 併用以

減少乳癌 p’t 之 estrogen，androgen 製造，每天1 g dose。

**Cholesterol**

↓

**ACTH ?**

**(-) Aminoglutethimide**

**pregnenolone**

Cholesterol

ACTH ?
(-) Aminoglutethimide

↓

pregnenolone → 17α-hydroxylase (-) ketoconazole

↓

progesterone

↓ 21β-hydroxylase

11-Deoxycorticosterone

↓ 11β-hydroxylase (-) ketoconazole

corticosterone

↓

Aldosterone

## 5. Ketoconazole

係antifungal imidazole衍生物，能抑制: 17-hydroxylase,

11β-hydroxylase.

∴(1) 代償性引起 ACTH↑

(2) Progesterone↑; Aldosterone ↓

(3) 抑制plasma renin 活性

→可供治療 Cushing Disease

200~1200 mg/天 (研究中)

→有 **hepatotoxicity**

## 6. Mifepristone ( RU 486 )

progesterone antagonist。Glucocorticoid receptor antagonist,

用於ectopic ACTH secretion 或 adrenal carcinoma

# 二、Mineralocorticoid Antagonist

- **Spironolactone:**

  1. 又叫Aldosterone antagonist

     Antikaliuretic diuretics

     Pot.Sparing

  2. 如血鈉↓、血鉀↑、Angiotensin↑

     則aldosterone release

     促進遠端腎小管$NA^+$-$K^+$ exchange

     ∴$Na^+$再吸收，鉀排出

  3. Spironolactone 與 aldosterone在遠端腎小管receptor 拮抗

     ∴增加$Na^+$、$Cl^-$排出↑，但$K^+$、$H^+$、ammonium 保留。

  4. 本品之onset 慢

5. 可使用於hyperaldosteronism(又叫conn’s syndrome)

(可能由腎上腺病 adenoma or 增殖hyperplasia 所引起，其症狀B.P.↑、肌肉無力、血鈉↑、血鉀↓、alkalosis、口渴)

*50~100 mg/天

6. 本品可用於肝硬化之水腫

(利尿作用常與Thiazide 併用)

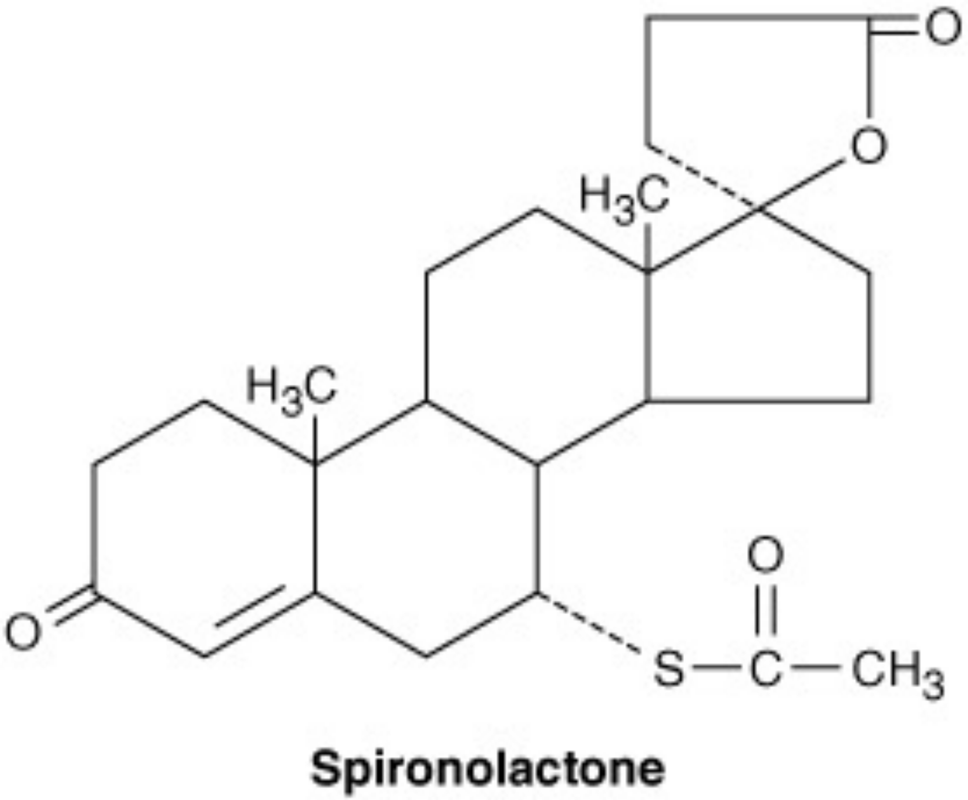
7. 副作用:

血鉀↑, mental confusion, 月經不正常, sedation, 頭痛, gynecomastia 男乳房增殖, rash

8. 本品另用於婦女多毛症 hirsutism

50~200 mg/天，可減少面部毛髮之密度，長度及生長率。

(由於androgen↑之多毛症)



## Aldosterone

↙ ↘

腎對鈉之再吸收　增加腎對鉀之排出

↓ ↓ ↓

血鈉↑　$H^+$ 排出　低血鉀症

↓ ↓ ↓

Polydipsia　鹼中毒　肌肉無力

↓口渴

Hypervolemia

血溶積↑

↓

心輸出↑

↓

B.P.↑

※ Aldosterone antagonist:

·Eplerenone

→治療高血壓 50~100 mg/d.

→比 Spironolatone 更具選擇性，

即對androgen receptor 無作用 。

·Drospirenone

→a progestin in an oral contraceptive

→對於 aldosterone 有拮抗作用